1,2,5-Thiadiazolo[3,4-*b*]pyrazines

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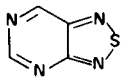
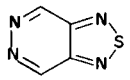
1,2,5-Thiadiazolo[3,4-*b*]pyrazine and its derivatives were prepared. Nucleophilic displacements of halogen atoms on the nucleus were reported.

As early as 1951, Schrage and Hitchings (1) reported derivatives of 1,2,5-thiadiazolo[3,4-*b*]pyrimidine, (I). In 1960, Sekikawa (2) reported the 4,7-dione of 1,2,5-thiadiazolo[3,4-*d*]pyridazine, (II). The fully aromatic system was reported in 1971 by Castle and Pichler (3). In 1970, Zolotova and Pesin (4), and Harts, de Roos and Salemink (5), independently reported 1,2,5-thiadiazolo-[3,4-*b*]pyridine, (III). After our work was finished (6), the 1,2,5-thiadiazolo[3,4-*b*]pyrazine ring system (IV), appeared in the literature (7). We would now like to report our work in the 1,2,5-thiadiazolo[3,4-*b*]pyrazine series. 2,3-Diamino-5,6-dichloropyrazine, (V), and 2,3-



I



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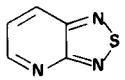

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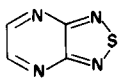
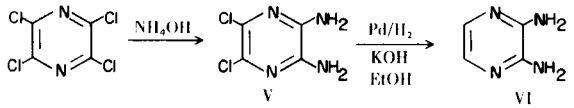


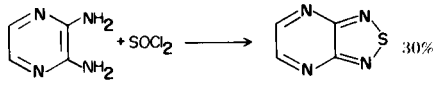
IV

diaminopyrazine, (VI), were prepared according to the method of Palamidessi and Luini (8). The formation

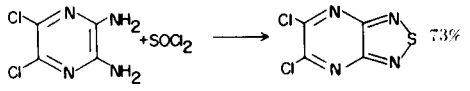


V VI

of the parent compound 1,2,5-thiadiazolo[3,4-*b*]pyrazine, (IV), and 5,6-dichloro-1,2,5-thiadiazolo[3,4-*b*]pyrazine, (VII), were straightforward:

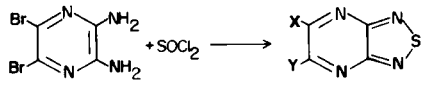


VI IV



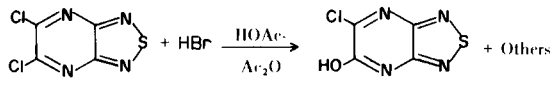
V VII

Tetrabromopyrazine was prepared by the method of Gulbenk (9), and was aminated under identical conditions as the chloro-compound to 2,3-diaminodibromopyrazine (10). Preparation of 5,6-dibromo-1,2,5-thiadiazolo[3,4-*b*]-pyrazine (IX) was successful only after many attempts. Direct reaction of diaminodibromopyrazine with thionyl chloride resulted in the formation of the thiadiazole ring and chlorine exchange:



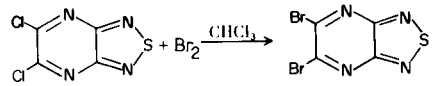
X Y Cl.
X Y Br
X = Cl, Y = Br.

Use of thionyl bromide in place of thionyl chloride gave only tar. Exchange of chlorine with hydrogen bromide resulted in hydrolysis, even in acetic acid-anhydride mixture.



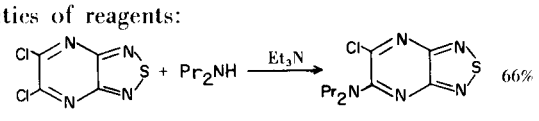
VIII

Finally, a sample was prepared by halogen exchange with bromine:



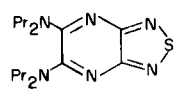
IX

The chlorine atoms of VII can be replaced easily. When an amine is used as a nucleophile, one or both chlorine atoms can be replaced, depending upon the quantities of reagents:



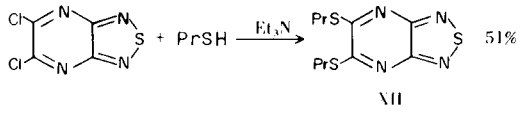
I 1.1 X

0.5 1.1



XI

When propanethiol was employed as a nucleophile, *bis*-propylthio-1,2,5-thiadiazolo[3,4-*b*]pyrazine, (XII), was the sole product, regardless of the reagent ratio:



1	1	29%
1	2	47%

In view of the reactivity of the chlorine atoms on VII, other displacement reactions are being studied currently in our laboratory.

EXPERIMENTAL

Melting points were not corrected. The ir spectra were recorded with a Beckman IR-5 Spectrophotometer in Nujol. The uv spectra were determined with a Cary-14 Spectrophotometer.

Preparation of 1,2,5-Thiadiazolo[3,4-*b*]pyrazine (IV).

In a reaction flask were mixed 11.0 g. (0.1 mole) of 2,3-diaminopyrazine, 23.8 g. of thionyl chloride and 100 ml. of xylene. The whole mixture was heated to boiling under reflux for 8 hours. After cooling, the reaction mixture was concentrated under reduced pressure and the residue extracted with benzene. The benzene solution was decolorized with charcoal and evaporated to dryness to yield 4.2 g. (30%) of product, m.p. 162-165°; ir (micron): 6.66(m), 7.45(m), 7.84(m), 8.36(s), 9.90(s), 10.55(s), 11.44(s), 12.21(m); uv λ max (chloroform): 304 (ε, 12,380), 311 (ε, 18,420), 317 (ε, 20,230), 324 (ε, 23,250).

Anal. Calcd. for $C_4H_2N_4S$: C, 34.8; H, 1.5; N, 40.6. Found: C, 34.8; H, 1.8; N, 40.7.

Preparation of 5,6-Dichloro-1,2,5-thiadiazolo[3,4-*b*]pyrazine (VII).

In 150 ml. of xylene were mixed 17.9 g. (0.1 mole) of 2,3-diamino-5,6-dichloropyrazine, and 1 ml. of pyridine. To this mixture was added, slowly with stirring, 26.2 g. (0.22 mole) of thionyl chloride. The whole mixture was heated to boiling under reflux for 7 hours. The mixture was evaporated to dryness under reduced pressure, washed with hexane and filtered. The solid was decolorized with silica gel, recrystallized from carbon tetrachloride-benzene mixture to give a total of 15.2 g. (73.5%) of product, m.p. 180-182°; ir (micron): 6.61(ω), 7.69(ω), 8.01(m), 8.56(s), 9.7(m), 9.91(s), 10.01(s), 11.26(m), 12.10(m); uv λ max (chloroform): 330 (ε, 18,820), 336 (ε, 18,820).

Anal. Calcd. for $C_4Cl_2N_4S$: C, 23.2; H, 0.0; N, 27.1. Found: C, 23,0; H, 0.4; N, 26.8.

Preparation of 5,6-Dibromo-1,2,5-thiadiazolo[3,4-*b*]pyrazine (IX).

A mixture of 6.2 g. (30 mmoles) of 5,6-dichloro-1,2,5-thiadiazolo[3,4-*b*]pyrazine and 19.2 g. (120 mmoles) of bromine in 150 ml. of chloroform was heated to boiling under reflux for 96 hours with a clear glass heat-lamp. After 72 hours, the solution became clear, an additional 19.2 g. of bromine was added. At the end of the reaction, the excess bromine and solvent were removed under reduced pressure and the residue recrystallized from benzene-carbontetrachloride (1:1) twice to give 4.8 g. (54%) of product, m.p. 150-151°; ir (micron): 6.57(ω), 7.65(m), 8.00(m), 8.11(ω), 8.85(s), 10.09(s), 10.21(m), 11.38(m), 12.16-(m); uv λ max (chloroform): 338 (ε, 19.880), 350 (ε, 20,580).

Anal. Calcd. for $C_4Br_2N_4S$: C, 16.2; Br, 54.0; N, 18.9. Found: C, 16.2; Br, 54.1; N, 19.0.

Preparation of 5-Chlror-6-(di-*n*-propylamino)-1,2,5-thiadiazolo-[3,4-*b*]pyrazine (X).

In 25 ml. of toluene were mixed 4.15 g. (20 mmoles) of 5,6-dichloro-1,2,5-thiadiazolo[3,4-*b*]pyrazine, 2.22 g. (22 mmoles) of di-*n*-propylamine, and 2.22 g. (22 mmoles) of triethylamine. The whole was heated to boiling under reflux for 4 hours, cooled and filtered to remove triethylamine hydrochloride. The filtrate was concentrated and distilled at ~ 160/0.1 mm. The distillate solidified on standing and was recrystallized from hexane to give 3.4 g. (66%) of product, m.p. 63-64°; ir (micron): 6.46(s), 6.97(m), 7.30(m), 7.48(ω), 7.61(ω), 7.98(m), 8.60(m), 9.31(s), 9.57(ω), 9.74(ω), 10.5(ω), 11.96(s), 12.38(s).

Anal. Calcd. for $C_{10}H_{14}ClN_5S$: C, 44.2; H, 5.2; N, 25.8. Found: C, 44.2; H, 5.1; N, 25.7.

Preparation of 5,6-*bis*-(Di-*n*-propylamino)-1,2,5-thiadiazolo[3,4-*b*]-pyrazine (XI).

In 75 ml. of toluene were mixed 10.4 g. (0.05 mole) of 5,6-dichloro-1,2-5-thiadiazolo[3,4-*b*]pyrazine, 11.1 g. (0.11 mole) of di-*n*-propylamine and 11.1 g. (0.11 mole) of triethylamine. The reaction mixture was heated to boiling under reflux for 6 hours, and filtered to remove triethylamine hydrochloride. The filtrate was evaporated to dryness to give a black oil. The black oil was flush distilled at 0.1 mm. to a red oil, which solidified. It was recrystallized form hexane to give 8.6 g. (51%) of product, m.p. 54-56°; ir (micron): 6.50(m), 6.70(s), 7.47(ω), 7.70(ω), 7.98(m), 8.12(m), 8.62(m), 8.78(m), 9.20(m), 11.68(s), 12.64(s).

Anal. Calcd. for $C_{16}H_{28}N_6S$: C, 57.1; H, 8.4; N, 25.0. Found: C, 57.1; H, 7.9; N, 25.0.

Preparation of 5,6-*bis*-(*n*-Propylthio)-1,2,5-thiadiazolo[3,4-*b*]-pyrazine (XI).

In 250 ml. of benzene were mixed 4.15 g. (20 mmoles) of 5,6-dichloro-1,2,5-thiadiazolo[3,4-*b*]pyrazine and 3.8 g. (50 mmoles) of propanethiol. The mixture was cooled to 15-20° while 5 g. (50 mmoles) of triethylamine in 20 ml. of benzene was added slowly. The whole was stirred at room temperature for 6 hours. Triethylamine hydrochloride which formed was removed by filtration. The filtrate was concentrated and the residue recrystallized from hexane to give 2.7 g. (47%) of product, m.p. 69-70°; ir (micron): 6.60(ω), 7.25(s), 7.55(ω), 7.98(ω), 8.66(s), 9.68(s), 11.08(ω), 11,35(ω), 12.15(s); uv λ max (chloroform): 366 (ε, 17,070), 383 (ε, 22,860).

Anal. Calcd. for $C_{10}H_{14}N_4S_3$: C, 41.9; H, 4.93; N, 19.6. Found: C, 42.0; H, 4.6; N, 19.8.

The reaction was repeated with 5.2 g. (25 mmoles) of 5,6-dichloro-1,2,5-thiadiazolo[3,4-*b*]pyrazine, 1.9 g. (25 mmoles) of propanethiol and 2.5 g. (25 mmoles) of triethylamine in 110 ml. of benzene. The same *bis* substituted product was obtained in 29% yield. It was identified by ir and tlc.

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